Original Article

Safely Diagnosing Clinically Significant Penicillin Allergy Using Only Penicilloyl-Poly-Lysine, Penicillin, and Oral Amoxicillin

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What is already known about this topic? Penicillin skin testing can be performed in advance of need. The rate of positive penicillin skin test results has been falling.

What does this article add to our knowledge? Penicillin skin testing can be safely done using only penicilloyl-poly-lysine and penicillin G, if followed by an oral amoxicillin challenge. The minor determinants penicilloate, penilloate, and amoxicillin are not currently needed as skin test reagents.

How does this study impact current practice management guidelines? It may be possible to simplify current practice guidelines.

BACKGROUND: Penicillin skin testing is rarely used to undiagnose penicillin "allergy" in the United States, partially because of concern that commercially available materials are inadequate.

OBJECTIVE: We determined whether skin testing with only commercially available penicilloyl-poly-lysine and penicillin followed by an oral amoxicillin challenge, if skin test-negative, can safely identify clinically significant penicillin allergy.

METHODS: Five hundred sequential persons with positive history of penicillin "allergy" were evaluated by skin testing with penicilloyl-poly-lysine and penicillin between June 8, 2010, and March 29, 2012. All persons with negative skin tests were given an oral amoxicillin challenge and observed for 1 hour.

RESULTS: Persons undergoing penicillin allergy testing were representative of all health plan members with penicillin allergy. Only 4 persons (0.8%; 95% CI, 0.32%-2.03%) had a positive skin test result. Only 4 persons (0.8%; 95% CI, 0.32%-2.03%) had an acute objective oral amoxicillin challenge reaction. Fifteen persons (3.0%; 95% CI, 1.83%-4.98%) had subjective oral challenge reactions, either acute transient itching or dizziness. All were women and 11 (73.3%) had multiple drug intolerance syndrome. None had severe reactions or objective signs. These were not considered to be positive challenge reactions. Sixty-eight subjects (13.6%) who were negative on testing were exposed to 88 courses of penicillins during 90 days of follow-up. New reactions were reported after 4 courses (4.5%), 3 (75%) occurring in subjects with multiple drug intolerance syndrome.

CONCLUSIONS: Penicillin skin testing, using only penicilloyl-poly-lysine and penicillin, followed by oral amoxicillin challenge, if negative, can safely identify clinically significant IgE-mediated penicillin allergy in patients who use health care in the United States at this time. © **2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:258-63)**

Key words: *Adverse reaction; Allergy; Antibiotic; Amoxicillin; Oral challenge; Multiple drug intolerance syndrome; Penicillin; Skin test; Penicilloyl-poly-lysine*

When penicillin skin testing was first done on a large scale in the 1960s through the 1990s, approximately 10% of persons with a history of penicillin "allergy" in the United States have had positive penicillin skin test results, with lower rates seen in outpatients and in children and higher rates seen in hospitalized populations.[1,2] Penicillin skin testing with the use of a complete panel, including the minor determinants, penicilloate, penilloate, and amoxicillin, identifies approximately 15% more positive persons over what would be seen with the use of the major determinant, penicilloyl-poly-lysine, and one minor determinant, native penicillin, alone.[3] Our group has performed penicillin skin testing on >4000 persons between November 16, 1994, and June 7, 2010, with the use of a complete panel of penicillin skin test reagents, including penicilloyl-poly-lysine, penicillin, penilloate, penicilloate, and amoxicillin.[4-6] Since about mid-2006, we have routinely given an oral amoxicillin challenge to subjects with a negative skin test. It has been noted in the United States that the frequency of positive

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Abbreviation used
MDIS- Multiple drug intolerance syndrome

penicillin skin tests in the 2000s has, on average, been significantly lower than reported in previous decades.[7-10] We have previously published data that have shown a steadily falling rate of positive penicillin skin test results between 1995 and 2007.[4]

The proportions of the population who think they are "allergic" to all classes of antibiotics raises with increasing age.[10,11] Despite approximately 7.8% of Americans who use health care with a history of penicillin allergy, penicillin skin testing is rarely used to undiagnose penicillin allergy in the United States. Only 27,665 ampules of commercially prepared penicilloyl-poly-lysine, Pre-Pen, sold in the United States during 2011. The present study accounts for at least 1% of the penicillin allergy skin testing done in the United States during 2011. Many allergists are concerned that the commercially available penicillin skin test materials, penicilloyl-poly-lysine and native penicillin, may be inadequate. Allergists in the United States have never had commercial access to a complete panel of penicillin skin test reagents. Some groups have tried to produce penicilloate and/or penilloate, but rarely were these preparations adequately characterized.[12] On the basis of anecdotal reports, most of the persons who have had penicillin skin testing in the United States were only effectively skin tested with penicilloyl-poly-lysine and penicillin. In addition, allergists in private practice in the United States are usually not reimbursed enough to cover the cost of the current commercially available skin test materials, if they only skin test and do not perform an oral challenge. Complicating this picture was the lack of Pre-Pen between September 2000 and November 2001 and again between September 2004 and November 2009. Many allergists in fellowship training over the past decade performed no penicillin skin testing during their training, and many allergists in practice got out of the habit. Thus, the only centers in the United States to test hundreds of persons for penicillin allergy per year during the past decade have been vertically integrated health care programs such as the Mayo Clinic and Kaiser Permanente.[4,7]

We now report that clinically significant IgE-mediated penicillin allergy can be safely diagnosed without using penicilloate, penilloate, or amoxicillin for skin testing, if an oral amoxicillin challenge is used as part of the testing protocol.

METHODS

This study was reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board. The Kaiser Permanente Health Care Program has always maintained a single comprehensive medical record for each member. The medical record since 2007 has been completely electronic. This study complies with the European Academy of Allergy and Clinical Immunology position paper on nomenclature for allergy.[13]

Study subjects consisted of all patients tested for penicillin allergy, either as outpatients or in the hospital, by the San Diego Kaiser Permanente Allergy Department between June 8, 2010, and March 29, 2012. Data were both prospectively and retrospectively collected. All patients were referred for penicillin allergy testing by their treating physicians. All patients in this study had their penicillin skin testing and oral amoxicillin challenges performed by registered nurses. This study includes 242 persons who have been partially reported on previously in an editorial.[14] An allergy to penicillin was defined as any penicillin class antibiotic allergy entry in the drug allergy section of the electronic medical record. Persons with a history of toxic epidermal necrolysis, Stevens Johnson syndrome, hemolytic anemia, hepatitis, nephritis, or oral and/or skin blisters associated with or attributed to the previous use of a penicillin class antibiotic were not offered penicillin allergy testing. It was strongly recommended that these persons continue to avoid all penicillin class antibiotics. All subjects tested had a history of penicillin allergy according to anaphylaxis, respiratory problems, hives, other rashes, local swelling at the site of injection, gastrointestinal symptoms, unknown symptoms, or other symptoms not specifically excluded as noted above, occurring after exposure to a penicillin class antibiotic. Index symptoms and time since reaction was determined by chart review where possible, but they were mostly supplied by the patient at the time of the testing. A single investigator (E.M.) reviewed text fields in the electronic medical records when necessary.

Testing for penicillin allergy was performed as follows. All patients had skin testing with the major determinant penicilloyl-poly-lysine and the minor determinants penicillin and amoxicillin. We used amoxicillin as a skin test reagent in the present report only to collect data to compare with recent European reports. Penicilloyl-poly-lysine (Pre-Pen) was obtained from ALK (Round Rock, Tex) and was used per the package insert. The penicillin used was sodium penicillin G, approved by the Food and Drug Administration for intravenous use, diluted to 0.01 molar, or 5941 U/mL, in buffered saline at pH 7.4. Single-use vials were sterilely produced, stored at −70°C, and thawed only once before use. The amoxicillin used was sodium amoxicillin (A8523; Sigma-Aldrich, Indianapolis, Ind), prepared as previously described in detail to a final concentration of 0.01 molar, or 3.65 mg/mL, in buffered saline at pH 7.4.[12] A buffered saline-negative control and a histamine,1 mg/mL for prick tests and 0.1 mg/mL for intradermal tests, positive control were placed at the start of each round of tests. Drops of each reagent were placed on the outer surface of the upper arm and pricked with a different DUOTIP-TEST device for each drop. After a 15-minute waiting period, skin prick reactions were read and recorded. The mean diameter of the wheal over the mean diameter of the flare or surrounding erythema was measured in millimeters. As noted in the Pre-Pen package insert, a positive response to skin prick consisted of a wheal of >5 mm in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine. If the skin prick tests were negative, then intradermal testing was performed on the outer surface of the other upper arm. If the skin prick tests were positive, then no intradermal testing was done.

Intradermal testing was done with the same concentrations of penicilloyl-poly-lysine, penicillin, and amoxicillin as noted in the previous paragraph. Only a single intradermal test was done for each material. Individual 27-gauge tuberculin syringes were used to place 0.02 mL of each reagent intradermally. Intradermal tests were also read and recorded after 15 minutes. As noted in the Pre-Pen package insert, positive intradermal responses again consisted of a wheal of ≥ 5 mm in diameter with surrounding erythema greater than the wheal, a negative response to the control solution, and a positive response to histamine. Patients with positive responses to the control solution or negative responses to the histamine control were considered not to be tested and told to continue to avoid penicillins.

An oral amoxicillin challenge was given to all persons with negative skin test. The amoxicillin was given in a single 250-mg dose, unless the subject was younger than 4 years old, then 125 mg was used. Subjects were observed for 1 hour after the oral challenge. Isolated itching or dizziness associated with the oral challenge, without other associated objective findings such as rash or change in blood pressure, were not considered positive challenge reactions, but were recorded. Study subjects reported all delayed reactions they considered significant over the phone. All adverse drug reactions resulting in a new drug allergy entry in the 100 days after testing were tabulated.

All San Diego area health plan members who had at least 1 medical care visit during the study interval served as a control population to determine whether patients tested for penicillin allergy were representative of all health plan members with a history of penicillin allergy. The age for control health plan members was defined by their age at their health care visit closest to the middle of the study period, May 4, 2011. Health care utilization was determined for both tested and control populations over the interval ± 90 days from the date of their penicillin allergy test or the health care visit used to determine age. Multiple drug intolerance syndrome (MDIS) was defined as 3 or more unrelated drug class allergies noted in the medical record.[11]

Hypothesis testing for continuous variables was by means of the Student *t*-test and for categorical variables by the chi-square test. Nominal statistical significance was set at a $P = .05$. All statistical analyses were performed with SAS statistical software (Cary, NC).

RESULTS

Study subject and overall health plan demographics are presented in Table I.

The index penicillin class antibiotic-associated adverse reaction in tested subjects was a nonhive rash in 204 (40.8%), hives/angioedema in 169 (33.8%), unknown in 72 (14.4%), other adverse reaction in 41 (8.2), and anaphylaxis in 14 (2.8%). The time to onset of index adverse reaction with the start of the last therapeutic exposure of penicillin class antibiotic was unknown in 152 (30.4%), 1 to 24 hours in 113 (22.6%), >73 hours in 104 (20.8%), 25 to 72 hours in 79 (15.8%), and <1 hour in 52 (10.4%) participants. The time since the index reaction and skin testing was 20.2 ± 19.7 years. There were 22 persons with unknown time since index reactions. The interquartile ranges for those with known times since index reactions were 0 to 2.6 years, 2.6 to 13.0 years, 13.0 to 40.0 years, and 40.0 to 66.4 years. These data are not available for health plan members with a history of penicillin allergy who did not undergo penicillin skin testing.

Positive skin test and oral challenge results are presented in Table II. There were 4 study subjects (0.8%; 95% CI, 0.3%-2.0%) with positive penicillin skin test results. No positive amoxicillin skin test results were observed; no penicillin skin test-associated adverse reactions were observed. There were 4 study subjects (0.8%; 95% CI, 0.32%-2.03%) with significant objective challenge reactions to acute oral amoxicillin. All patients with objective challenge reaction were treated with oral antihistamines and all resolved within 1 hour. The time since index reaction was relatively short in 3, intermediate in 2, and extremely long in 3 of the subjects with confirmed IgE-mediated penicillin allergy. No sex predilection for confirmed penicillin allergy; 5 (62.5%) were women ($P = .7266$).

Two significant delayed-onset adverse reactions were reported. One was in an 80-year-old woman with MDIS and consisted of gastrointestinal upset, starting approximately 12 hours after the oral challenge. The reaction did not require treatment. The second was in a 58-year-old woman with MDIS who noted nausea and migraine, starting about 12 hours after the oral challenge. She took her usual migraine therapy. No delayed onset, potentially T-cell mediated, rashes were seen in 495 oral challenges.

Fifteen study subjects (3.0%; 95% CI, 1.8%-4.9%), all women, reported acute subjective reactions during the 1-hour observation after the oral challenge. These data are displayed in Table III. Thirteen persons had isolated itching and 2 persons had isolated dizziness. None had any other clinically significant acute, persistent, or delayed reactions, and none had visible hives, change in blood pressure, or other objective signs. None required any therapy. There were 11 persons (73.3%) in this group with MDIS, and 9 (60.0%) of them reported 4 or more unrelated drug class intolerances. In this group of 15 subjective reactors 1 received 1 course of dicloxacillin and 2 received 1 course of amoxicillin during the 90-day follow-up period. Two tolerated their therapeutic exposures to penicillin class antibiotics and one, a 14-year-old girl with MDIS, had a delayed onset rash, on the face only, starting 2 days after amoxicillin given for an upper respiratory infection.

At 100 days after skin testing 20 study subjects had an active penicillin allergy notation in their medical record. This included the 8 subjects with confirmed IgE-mediated penicillin allergy. Among the remaining 12 persons, 4 had a new reaction after a therapeutic exposure to penicillin class antibiotics. There were 69 study subjects (13.8%) exposed to 88 courses of therapeutic penicillins, 55 (79.7%) exposed to 67 (76.1%) courses of amoxicillin or amoxicillin clavulanate, during the 90 days after skin testing. These 4 cases represented a 4.5% new reaction rate per course. The first case was the 14-year-old girl described above. The second was a 54-year-old woman with MDIS and underlying common variable immunodeficiency, who made no IgE, who had a delayed onset rash after amoxicillin clavulanate. The third person was a 55-year-old woman with MDIS who tolerated 3 courses of oral amoxicillin and then had a rash 4 weeks into a course of intravenous oxacillin. The final reaction occurred in a 69-year-old man with metastatic cancer who had a delayed onset rash after intravenous penicillin. He had no other known drug allergies. Two of the subject reactors (13.3%) still had penicillin allergy listed in their medical records. One of the two delayed-onset objective reactors, the one with the migraine and MDIS, still had penicillin allergy listed in her medical record. The remaining 5 persons represented errors in charting.

Twenty-two study subjects (4.4%) were tested and challenged in the hospital. Seven study subjects (1.4%) had an acute diagnosis of syphilis, all were negative for skin test and oral challenge. All then received 2.4 million units of intramuscular penicillin, and no adverse reactions were noted.

DISCUSSION

We again document a low, and falling, rate of positive results for penicillin skin tests, consistent with our previous reports[4,5] and other recent reports from groups in the United States.[7,9] Interestingly, there was a falling rate of positive penicillin skin test results noted in the 1971 report by Adkinson et al[15] who studied inpatients at Johns Hopkins. They found lower rates of positive

TABLE I. Study subject demographics compared with all health plan members using medical care during the study period

	Penicillin skin test cases (n = 500)	Health plan members with history of penicillin allergy (n = 51,978)	Health plan members with no penicillin allergy history (n = 478,656)
Female, no. (%)	317 (63.4)	33,457 (64.4)	252,993 (52.9)
Age (y)*			
Mean ± SD	40.7 ± 26.5	46.6 ± 22.2	38.9 ± 22.5
Q1, Q3	14.0, 62.9	29.0, 63.1	19.7, 56.4
Range	1.1 to 93.4	0.2 to 101.0	0.0 to 106.2
Ethnicity			
White, n (%)	329 (65.8)	31,134 (59.9)	226,656 (47.4)
Hispanic, n (%)	99 (19.8)	10,438 (20.1)	129,612 (27.1)
Black, n (%)	18 (3.6)	2,500 (4.8)	24,229 (5.1)
Asian/Pacific, n (%)	32 (6.4)	3,303 (6.4)	42,715 (8.9)
Multiple/other, n (%)	9 (1.8)	933 (1.8)	10,838 (2.3)
Unknown, n (%)	13 (2.6)	3,670 (7.0)	44,606 (9.3)
BMI†			
No.	447	46,311	408,716
Mean ± SD	25.4 ± 7.7	27.3 ± 7.1	26.5 ± 6.9
Days of health plan coverage,‡ mean ± SD‡	175.1 ± 21.8	173.7 ± 19.2	172.2 ± 21.3
Total outpatient health care visits,§ mean ± SD	8.4 ± 7.2	4.2 ± 4.6	3.4 ± 3.8
Total ED visits,§ mean ± SD	0.4 ± 0.8	0.2 ± 0.5	0.1 ± 0.4
Total hospital days,§ mean ± SD	1.2 ± 5.8	0.2 ± 1.8	0.2 ± 1.5
Total nonantibiotic prescriptions,§ mean ± SD	8.3 ± 10.1	5.8 ± 7.5	3.9 ± 6.0
Total antibiotic prescriptions,§ mean ± SD	1.8 ± 1.9	0.5 ± 1.0	0.4 ± 0.8
Total drug class allergies noted on index visit			
0, no. (%)	None	None	383,476 (80.1)
1, no. (%)	208 (41.6)	30,594 (58.9)	68,281 (14.3)
2, no. (%)	111 (22.2)	11,874 (22.8)	17,981 (3.8)
3, no. (%)	60 (12.0)	4,991 (9.6)	5,749 (1.2)
≥4, no. (%)	121 (24.2)	4,519 (8.7)	3,169 (0.7)
MDIS ≥3, no. (%)	181 (36.2)	9,510 (18.3)	8,918 (1.9)

BMI, Body mass index.
*Age at date of penicillin allergy testing or health care visit closest to May 4, 2011, if not tested.
†BMI at health care visit closest to the date of penicillin allergy testing or May 4, 2011, if not tested.
‡Total days of health plan coverage during the ±90 days from date of penicillin allergy testing or visit closest to May 4, 2011, if not tested, maximum possible days of health plan coverage = 180.
§Health care utilization during the ±90 days from date of penicillin allergy testing or visit closest to May 4, 2011, if not tested.

TABLE II. Positive skin test results and objective acute oral challenge reactions

Time since reaction (y)	Age (y)	Sex	Index reaction	Time to index reaction onset (h)	Skin test results	Oral challenge result
0.04	53.0	F	Anaphylaxis	<1	Negative	Hives at 50 min; hypertension
0.1	1.7	M	Rash	>73	Pre-Pen; ID 20/30	Not done
0.2	37.1	F	Hives	>73	Negative	Hives at 20 min
2.4	6.1	M	Rash	1-24	Negative	Hives at 60 min
4.3	5.3	F	Hives	1-24	Negative	Hives at 50 min
22.0	57.4	F	Cough	<1	Pre-Pen; ID 12/30	Not done
55.8	64.8	M	Angioedema	1-24	Pre-Pen ID 15/20	Not done
56.0	85.8	F	Angioedema	1-24	Penicillin; ID 8/12	Not done

results for penicillin skin test in 1969 and 1970 than in 1964 and 1965. It is unclear why currently fewer Americans with a history of penicillin allergy have positive results for penicillin skin tests, but it may be in part because of less parenteral exposure.

Adkinson et al[15] used 5 mm of wheal for intradermal tests as the positive cutoff in their 1971 report. In the major collaborative trial of penicillin skin testing that used minor determinants reported by Sogn et al[3] in 1992, a 1^+ positive skin test result was 4 to 6 mm of wheal, a 2^+ result was 7 to 9 mm, 3^+ was 10 to 13 mm, and 4^+ was 14 mm or greater. An unfortunate drift since then has called smaller skin test results positive. All of our positive results for skin tests in the present report consisted of wheals between 8 and 20 mm with flares between 12 and 30 mm. We again report lower rates of positive results of penicillin skin tests than groups that use 3 mm or 4 mm as the cutoff for a positive skin test result.[7,8] The present report provides further documentation

TABLE III. Subjective challenge reactions

Time since reaction (y)	Age (y)	Total drug class allergies (≥3 = MDIS)	Index reaction	Time to index reaction onset (h)	Oral challenge result (onset)
0.3	10.4	0	Rash	1-24	Itching (50 min)
5.1	24.6	2	Rash	25-72	Itching (25 min)
5.7	49.0	11; MDIS	Rash	<1	Itching (58 min)
7.8	65.8	4; MDIS	Hives	>73	Itching (15 min)
10.0	14.0	4; MDIS	Hives	Unknown	Itching (45 min)
10.0	60.7	5; MDIS	Rash	<1	Itching (20 min)
15.0	28.5	2	Shortness of breath	<1	Itching (immediate)
17.0	48.7	5; MDIS	Hives	<1	Itching (immediate)
30.8	50.7	6; MDIS	Rash	Unknown	Itching (25 min)
33.0	64.3	0	Hives	1-24	Itching (50 min)
40.0	77.2	5; MDIS	Faint	<1	Dizzy (55 min)
43.0	57.5	4; MDIS	Hives	>73	Dizzy (immediate)
52.0	68.4	4; MDIS	Hives	1-24	Itching (immediate)
63.2	75.2	2	Unknown	Unknown	Itching (20 min)
Unknown	43.0	4; MDIS	GI upset	Unknown	Itching (immediately)

that the use of a 5 mm or greater wheal as the definition of a positive penicillin skin test result, following the recommendation approved by the Food and Drug Administration in the package insert for Pre-Pen, reduces the number of apparent false-positive tests, specifically in women, compared with the use of 3 mm or greater[7] and safely identifies clinically significant IgE-mediated penicillin allergy when combined with an oral amoxicillin challenge, in subjects with a negative skin test.

We again note penicillin skin test—associated reactions much less frequently than groups that use much higher skin test reagent concentrations.[16,17] We used penicillin G at 0.01 molar or 5941 U/mL on the basis of our previous work.[12]

The present report is unique for recent large studies of penicillin allergy testing from the United States in that all persons with negative skin test received an oral amoxicillin challenge. We agree with Bousquet et al[18] as to the utility of oral amoxicillin challenges after negative penicillin skin tests, although we report a much lower frequency of clinically significant positive reactions to oral challenge.

Caubet et al[19] have shown the safety of using oral amoxicillin challenges in children with histories of beta-lactam—associated rashes, even challenging children with positive penicillin skin tests. They only noted 4 positive reactions to oral challenge in 11 children with positive skin test and 2 positive reactions to oral challenge in 77 children with negative skin test. They noted, as we did in the present report, that no reactions to oral amoxicillin challenge were life threatening, and none were more severe than the index reaction. Life-threatening reactions are always possible, particularly with parenteral penicillin exposures.

We now also show that subjective challenge reactions, including itching and dizziness, are strongly associated with MDIS (11/15 vs 108/477; $P < .0001$). It is important to document objective findings during oral challenge so persons are not needlessly continuing to avoid potentially safe and useful penicillin class antibiotics or subjected to the time and expense of going through an unnecessary desensitization procedure. We have previously reported that persons with subjective challenge reactions have tolerated full therapeutic penicillin courses and note 2 additional cases in this report.[12,20-22]

By not skin testing with a complete panel of minor determinants in this study, including penicilloate and penilloate, we could have missed up to 10% of the potential persons with positive skin test in our cohort, based on historic data from our group and others.[3,4,12] We currently have to test and oral challenge 1125 persons to find 9 positive results. If every person with positive minor determinant skin test was positive with oral challenge, we could avoid 1 positive oral challenge reaction for every 1125 persons tested by using the additional determinants. However, on the basis of our previously reported data on accidental oral penicillin use in persons with positive penicillin skin tests and data from intentional challenges in persons with positive penicillin skin tests from Sogn et al[3] and Caubet et al,[19] realistically only approximately one-third would be expected to be challenge positive. Thus, we would have to test approximately 3375 persons with a complete panel of reagents to avoid one additional positive reaction to oral amoxicillin challenge.

It is also comforting that all acute positive reactions to oral amoxicillin challenge we have seen have been relatively mild and easily treated with oral antihistamines. This is why our group stopped using penicilloate and penilloate for routine penicillin skin testing in mid-2010, despite still having >60 g each of pure penilloate and penicilloate stored lyophilized under argon in the dark at −70°C that we produced in 1994.[12] We used amoxicillin as a skin test reagent in the present report only to collect data to compare with recent European reports.[23] We noted no persons positive for amoxicillin skin tests in this cohort. The upper 95% CI for 0 positive results for skin amoxicillin tests in 500 sequential tests is 0.76%. Our group stopped using amoxicillin as a skin test reagent after enrollment in this study was completed.

We provide some of the first population-based data in this study that compares tested subjects with all health plan members with a history of penicillin allergy. The sex and ethnicity of our study subjects closely mirrored the general population with a history of penicillin allergy. Study subjects were slightly younger and higher health care users than all health plan members with a history of penicillin allergy. On the basis of our previous work, our study subjects would be expected to have slightly higher rates of positive results for penicillin allergy tests

compared with average health plan members with a history of penicillin allergy.[4]

Delayed onset reactions, mediated by non-IgE mechanisms such as T-cell sensitization, are not predicted by penicillin skin testing read at 15 minutes. Hives occurring up to 24 hours after an oral challenge can still be an IgE-mediated event.[21] Both types of reactions can be clinically significant and are good reasons to perform oral amoxicillin challenges after negative penicillin skin tests. No clinically significant delayed onset rashes were compatible with a T-cell—mediated mechanism reported in this cohort, although we have noted rare clinically significant delayed onset, potentially T-cell—mediated, rashes in previous cohorts.[5]

The "gold standard" for the quality of a penicillin allergy test protocol is the clinical result observed in test-negative patients who are given therapeutic courses of penicillin class antibiotics. We have previously shown that in routine clinical practice 1.5% of woman and 1.1% of men will report a new penicillin allergy after each use of a penicillin class antibiotic.[10] Higher rates of antibiotic-associated adverse reactions are seen in persons with MDIS.[11] We now know that only approximately 1 in 50 persons with penicillin allergy will be test positive. We have previously shown that patients with a history of penicillin allergy, who are negative for skin tests, will have an adverse reaction rate of approximately 2.9% per future therapeutic course of penicillin class antibiotic used. Interestingly, they will also have about an equal rate of adverse reaction associated with future therapeutic sulfonamide antibiotic use.[6] The 4.5% new adverse reaction rate per course of penicillin class antibiotic exposure we note in the present study is in line with these findings.

Ideally, allergists in the United States should be testing and challenging hundreds of thousands of persons annually to start to make a dent in our epidemic of overreported penicillin allergy. More than 20 million Americans have a history of an allergy to penicillin. Testing more would allow more appropriate use of relatively narrow-spectrum penicillin class antibiotics. It could also help identify those persons truly at risk for clinically significant IgE-mediated allergy and potentially improve overall health outcomes.

It is essential that commercially available penicilloyl-poly-lysine remain permanently on the market in the United States. Ideally, appropriate concentrations of prepackaged lyophilized penicillin should be marketed with the Pre-Pen to improve ease of use. Penicillin skin testing, using only penicilloyl-poly-lysine and penicillin, with appropriate positive test criteria, followed by an oral amoxicillin challenge, if negative for skin test, is a safe way to determine clinically significant IgE-mediated penicillin allergy.

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